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## **Efficacy and Safety of Long-Term Imatinib Therapy for Pulmonary Arterial Hypertension**

Speich, Rudolf ; Ulrich, Silvia ; Domenighetti, Guido ; Huber, Lars C ; Fischler, Manuel ; Treder, Ursula ; Breitenstein, Alexander

**Abstract:** Background: Antiproliferative strategies have emerged as a potential therapeutic option for pulmonary arterial hypertension (PAH). Objective: To evaluate the long-term efficacy and safety of imatinib. Methods: This is an observational study of 15 patients with idiopathic PAH (n = 13) or PAH associated with connective tissue disease (n = 2) treated offlabel with imatinib 400 mg daily. Pulmonary hypertensionspecific therapy was established in all patients (triple therapy in 10, dual therapy in 3, and monotherapy in 2 patients). Results: After 6 months, improvement in hemodynamics ( $p < 0.01$ ), functional class ( $p = 0.035$ ), and quality of life ( $p = 0.005$ ) was observed. After a median follow-up of 37 months, there was a sustained improvement in functional class ( $p = 0.032$ ), quality of life ( $p = 0.019$ ), and echocardiographic parameters of right ventricular function ( $p < 0.05$ ). Three patients (20%) presented with completely normal echocardiography, absent tricuspid regurgitation, and normal pro-brain natriuretic peptide levels, indicative of 'hemodynamic remission'. Of note, however, only 1 case was assessed by invasive hemodynamics. The overall 1- and 3-years survival was 100 and 90%, respectively. Two patients experienced a subdural hematoma (SDH), which in both cases resolved without sequelae. After careful consultation of the potential risks and benefits, all patients as well as a safety cohort of 9 subsequent cases decided to continue the imatinib therapy. After adjusting the target international normalized ratio (INR) to around 2.0, no further cases of SDH occurred during 50 patient-years. Conclusions: Long-term treatment with imatinib may improve the functional class and quality of life. Single cases might even attain hemodynamic remission. The occurrence of 5% SDH per patientyears is concerning. However, adjusting the INR to around 2.0 might obviate this complication.

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# Efficacy and Safety of Long-Term Imatinib Therapy for Pulmonary Arterial Hypertension

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For editorial comment see p. 513

## Key Words

Pulmonary arterial hypertension · Treatment · Imatinib · Adverse effects · Subdural hematoma

## Abstract

**Background:** Antiproliferative strategies have emerged as a potential therapeutic option for pulmonary arterial hypertension (PAH). **Objective:** To evaluate the long-term efficacy and safety of imatinib. **Methods:** This is an observational study of 15 patients with idiopathic PAH (n = 13) or PAH associated with connective tissue disease (n = 2) treated off-label with imatinib 400 mg daily. Pulmonary hypertension-specific therapy was established in all patients (triple therapy in 10, dual therapy in 3, and monotherapy in 2 patients). **Results:** After 6 months, improvement in hemodynamics (p < 0.01), functional class (p = 0.035), and quality of life (p = 0.005) was observed. After a median follow-up of 37 months, there was a sustained improvement in functional class (p = 0.032), quality of life (p = 0.019), and echocardiographic parameters of right ventricular function (p < 0.05). Three patients (20%) presented with completely normal echocardiography, absent tricuspid regurgitation, and normal pro-brain natriuretic peptide levels, indicative of 'hemodynamic remission'. Of note, however, only 1 case was assessed by invasive hemodynamics. The overall 1- and 3-year

survival was 100 and 90%, respectively. Two patients experienced a subdural hematoma (SDH), which in both cases resolved without sequelae. After careful consultation of the potential risks and benefits, all patients as well as a safety cohort of 9 subsequent cases decided to continue the imatinib therapy. After adjusting the target international normalized ratio (INR) to around 2.0, no further cases of SDH occurred during 50 patient-years. **Conclusions:** Long-term treatment with imatinib may improve the functional class and quality of life. Single cases might even attain hemodynamic remission. The occurrence of 5% SDH per patient-years is concerning. However, adjusting the INR to around 2.0 might obviate this complication. © 2015 S. Karger AG, Basel

## Introduction

There has been considerable expansion of the therapeutic options for patients suffering from pulmonary arterial hypertension (PAH) [1]. While in the past vasoconstriction has been the main target, antiproliferative strategies to reverse vascular remodeling have emerged as an

Rudolf Speich and Silvia Ulrich contributed equally to this paper.

important concept in the management of this rare and still often fatal disease. The 3 targeted pathways heretofore, i.e. prostaglandins, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, have – to a variable extent – some antiproliferative properties [2]. However, prevention or treatment of pulmonary arterial remodeling has been addressed almost exclusively in experimental settings and no direct evidence of such effects in humans has been demonstrated.

Among several growth factors involved in the abnormal migration and proliferation of pulmonary smooth muscle cells, platelet-derived growth factor (PDGF) has been identified as a key mediator in the pathogenesis of PAH. More than 10 years ago, Humbert et al. [3] were able to detect an increased expression of PDGF A-chain mRNA in the lung samples of 13 PAH patients. Subsequently, these findings have been confirmed by several other groups [4–7]. PDGF has the ability to induce the migration and proliferation of smooth muscle cells and fibroblasts and represents an important factor for the progression of fibroproliferative disorders including PAH [8].

In rats with monocrotaline-induced pulmonary hypertension, Schermuly et al. [7] demonstrated that administration of imatinib decreased PDGF-B expression in the pulmonary vasculature and prevented phosphorylation of the PDGF receptor. Treatment with imatinib starting 28 days after induction of the disease resulted in reverse remodeling with near normalization of the vascular muscularization and medial wall thickness. The elevated right ventricular pressure and right heart hypertrophy were drastically improved. Imatinib treatment resulted in 100% survival compared to only 50% in placebo-treated rats.

In light of these findings, the same group initiated imatinib therapy in a patient who had a deteriorating course despite triple therapy for idiopathic PAH yet refused lung transplantation [9]. Three months after the start of imatinib, the patient showed a dramatic improvement in functional class, 6-min walk distance (6MWD), and pulmonary hemodynamics. Subsequently, 3 other cases with a comparable response to imatinib have been reported [10, 11].

In the context of these preliminary data, we commenced an observational study to evaluate the efficacy and safety of long-term imatinib treatment in patients already on targeted PAH therapy. In order to thoroughly assess their clinical course, we performed a comprehensive follow-up of each patient, including a full hemodynamic evaluation at baseline and after 6 months of ther-

apy. Herein, we present the clinical course of our first consecutive 15 patients who completed at least a 6-month treatment period.

## Materials and Methods

The current observational study was conducted at the University Hospital Zurich beginning in February 2008. PAH was diagnosed according to international guidelines based on the presence of a mean pulmonary artery pressure (mPAP) >25 mm Hg and a pulmonary artery occlusion pressure <15 mm Hg [12]. The inclusion criteria for the current observational study were as follows: patients already on targeted PAH combination treatments and not having reached our therapeutic goals [adapted from the Paris Pulmonary Hypertension Program; O. Sitbon, pers. commun.], which consist of a cardiac index >2.8 liters/min/m<sup>2</sup>, NYHA functional class II, and a 6MWD >400 m. This observational study was formally approved by the local ethics committee, although according to Swiss regulation practice there is no need for ethical approval if off-label use of drugs is applied in orphan diseases.

Herein we describe our first 15 consecutive cases. The median follow-up time was 37 months [interquartile range (IQR) 28–46; range 8–60]. One case has already been presented elsewhere [13]. Imatinib was started at a dose of 200 mg/day, which was increased to 400 mg/day after about 2 weeks in all patients.

Baseline assessment and follow-up after 6 months of therapy included a thorough clinical examination, assessment of the NYHA functional class and 6MWD according to international guidelines [14], a full invasive hemodynamic evaluation, and exploration of the health-related quality of life using the German version of the CAMPHOR questionnaire [15]. This score ranges from 0 (best) to 80 (worst). The questionnaire could not be applied in 5 patients for linguistic reasons.

At the last time point of follow-up, only 1 patient underwent an invasive hemodynamic assessment [13]. In all other patients the mPAP was calculated from the systolic pressure gradient between the right ventricle and the right atrium determined by echocardiography according to the formula of Chemla et al. [16], i.e.  $mPAP = 0.61 \cdot (RV - RA + 5) + 2$ . Data on tricuspid annular plane systolic excursion and fractional area change were not available in 5 patients since their echocardiography was not performed at our institution.

After becoming aware of the fact that imatinib may contribute to the occurrence of subdural hematoma (SDH) in September 2011 [17], we decided firstly to keep the INR around 2.0, and secondly to obtain written informed consent from the patients willing to continue imatinib therapy, emphasizing the risk of SDH.

To thoroughly assess the willingness of our patients to continue imatinib therapy despite being aware of the increased risk of SDH, we confronted them with a worst-case scenario concerning the morbidity and mortality of SDH. For that purpose, we performed a comprehensive literature review of more than 4,000 patients suffering from SDH. To calculate the 95% CI for morbidity and mortality due to SDH given in the literature, the exact Poisson confidence limit was used.

The analysis revealed a weighted average morbidity and mortality of SDH of 0.7% (95% CI 0.06–1; range 0–8) and 0.4% (95% CI 0.2–0.6; range 0–3), respectively [18–21]. Patients were con-

fronted with a worst-case scenario of SDH by using not the upper 95% CI but the upper ranges, i.e. an annual morbidity of up to 8% and a mortality of up to 3%, respectively.

The greatest difficulty was in presenting to the patients the usual clinical course of PAH. Most patient series give only data on survival and NYHA functional class, which would not have been illustrative enough. In addition, 10 patients were already on triple-drug therapy, including 6 patients on intravenous prostanoids. Moreover, 5 patients were aged >65 years, and another 5 would even have been candidates for lung transplantation according to the current guidelines. In fact there are no data whatsoever about the usual clinical course for such a seriously diseased patient population.

Furthermore, we included our next 9 cases followed up until June 2014 to perform an extended safety assessment of imatinib in PAH. Thereby we could increase our overall observation time up to 76 patient-years. The clinical course of these 9 patients, however, was not assessed as comprehensively as that of the initial cohort.

Data are given as medians with interquartile ranges, total ranges, or 95% CI as appropriate. Statistical analysis of continuous variables was performed using the Wilcoxon signed-rank test and the Kruskal-Wallis test as appropriate. Changes in NYHA functional class were assessed by comparing the number of patients in NYHA class I–II and III–IV using Fisher's exact test.  $p < 0.05$  was considered statistically significant.

## Results

### *Efficacy Parameters at 6 Months*

The demographics, treatment with targeted therapies, and details of imatinib therapy of the 15 consecutive patients are shown in table 1. Notably, 10 patients were already on triple-drug therapy, including parenteral prostanoids in 6 patients. Three patients were receiving combination therapy with bosentan and sildenafil, and 2 patients with features of pulmonary veno-occlusive disease tolerated neither sildenafil nor prostanoids.

All patients completed the 6-month treatment period. The main results in all of these 15 patients at baseline and after 6 months are presented in table 2. The 6MWD remained at a median of 458 m (IQR 411–520). The NYHA functional class improved significantly ( $p = 0.035$ ). Seven patients improved by 1 class, and overall 7 patients were in class II after 6 months (fig. 1). None of the patients deteriorated or remained in class IV. In addition, we observed a significant improvement (by 9 points) in health-related quality of life ( $p = 0.005$ ).

All except 1 patient underwent a complete invasive hemodynamic assessment by right heart catheterization at baseline and after 6 months of therapy (table 2). These data showed a significant improvement in mPAP, cardiac index, pulmonary vascular resistance (PVR), and mixed

**Table 1.** Demographics, pretreatment, and details of imatinib therapy

|  |            |
|--|------------|
| Patients   | 15         |
| Age, years   | 53 (39–69) |
| Range  | 22–74      |
| Females  | 11         |
| Diagnosis  |            |
| Idiopathic PAH <sup>a</sup>  | 13         |
| Connective tissue disease  | 2          |
| Duration of targeted therapy before imatinib, months                 | 43 (22–71) |
| Range  | 6–97       |
| Targeted therapy at imatinib baseline                                |            |
| Bosentan   | 2          |
| Bosentan and sildenafil  | 3          |
| Bosentan, sildenafil, and inhaled iloprost                           | 4          |
| Bosentan, sildenafil, and intravenous iloprost                       | 6          |
| Follow-up time of imatinib therapy, months                           | 37 (28–46) |
| Range  | 8–60       |
| Time to permanent cessation of imatinib therapy, months <sup>b</sup> | 8          |
| Length of temporary interruption of imatinib, months <sup>c</sup>    | 15, 35     |

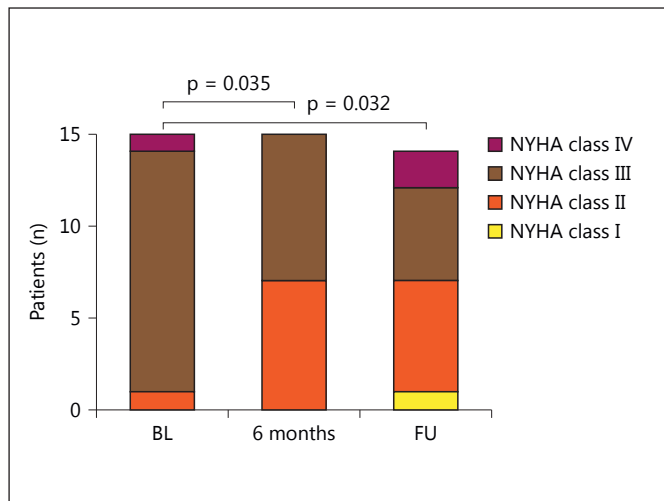
Values are presented as medians (IQR) or numbers unless otherwise stated. <sup>a</sup> Features of veno-occlusive disease in 2 patients. <sup>b</sup> In 1 patient. <sup>c</sup> In 2 patients.

venous oxygen saturation. Only 1 patient did not undergo right heart catheterization after 6 months. However, when assessed after 42 months on imatinib, and notably without any other changes in therapy, her PVR had decreased from 2,078  $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$  at baseline to 970  $\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ .

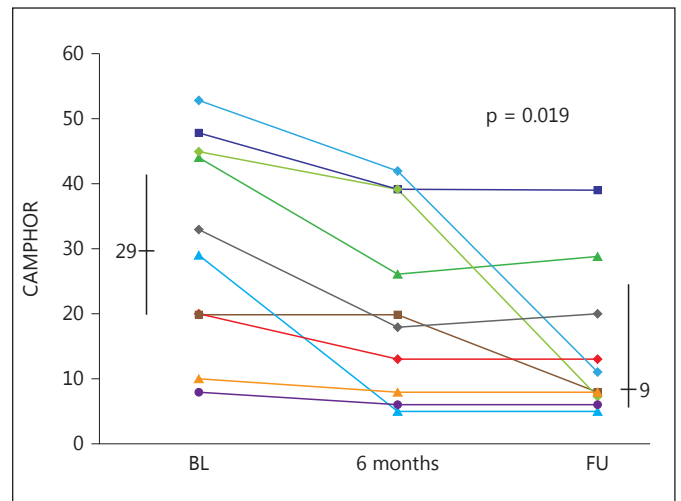
### *Long-Term Outcome*

All patients completed the first 6-month period on imatinib therapy and continued it thereafter, except for 1 patient who definitely stopped imatinib after 8 months because of mild diffuse musculoskeletal complaints and the lack of a subjective benefit.

Two patients temporarily interrupted imatinib therapy because of the lack of a subjective benefit ( $n = 1$ ) and nonspecific side effects ( $n = 1$ ). However, both of them resumed imatinib therapy after 15 and 35 months, respectively, because of a deteriorating clinical course. Notably, at the time of discontinuing imatinib, the former patient had become oxygen independent and her CAMPHOR score had improved from 20 to 13. Only a few months later, the patient again needed supplemental oxygen (4 liters/min) and her CAMPHOR score deteriorated



**Fig. 1.** Improvement in functional class from baseline (BL) to 6 months and the last follow-up visit (FU).



**Fig. 2.** Course of the health-related quality of life assessed by the CAMPOR questionnaire. Data are given as medians and IQR. BL = Baseline; FU = last follow-up visit. The questionnaire could not be applied in 5 patients for linguistic reasons.

**Table 2.** Efficacy parameters before and after 6 months of imatinib therapy (n = 15)

| Characteristics                                       | Baseline      | After 6 months of imatinib therapy | p      |
|---|---------------|------------------------------------|--------|
| 6MWD, m   | 469 (413–514) | 458 (411–520)                      | 0.820  |
| NYHA class (II/III/IV), n                             | 1/13/1        | 7/8/0                              | 0.035  |
| CAMPOR score  | 29 (20–44)    | 20 (11–33)                         | 0.005  |
| Heart rate, beats/min                                 | 80 (74–89)    | 82 (76–89)                         | 0.950  |
| Mean blood pressure, mm Hg                            | 82 (78–85)    | 80 (76–87)                         | 0.682  |
| Right heart catheterization (n = 14) <sup>a</sup>     |               |                                    |        |
| Right atrial pressure, mm Hg                          | 7 (4–9)       | 6 (4–10)                           | 0.812  |
| Mean pulmonary artery pressure, mm Hg                 | 53 (42–63)    | 42 (32–56)                         | 0.006  |
| Cardiac index, l/min/m <sup>2</sup>                   | 2.8 (2.6–2.9) | 3.4 (3.0–4.3)                      | 0.008  |
| Pulmonary vascular resistance, dyn•s•cm <sup>-5</sup> | 644 (585–854) | 429 (318–526)                      | <0.001 |
| Pulmonary artery occlusion pressure, mm Hg            | 11 (7–13)     | 10 (8–11)                          | 0.734  |
| Arterial oxygen saturation, %                         | 90 (89–92)    | 94 (91–95)                         | 0.115  |
| Mixed venous oxygen saturation, %                     | 62 (58–67)    | 69 (65–72)                         | 0.006  |

Values are presented as medians (IQR) unless otherwise stated. <sup>a</sup>One patient had no right heart catheterization after 6 months, but after 42 months on imatinib her pulmonary vascular resistance decreased from 2.078 dyn•s•cm<sup>-5</sup> at baseline to 970 dyn•s•cm<sup>-5</sup>.

to 30 points. In retrospect, her symptoms leading to the interruption of imatinib could have been attributed to an incipient nondiagnosed diabetes mellitus.

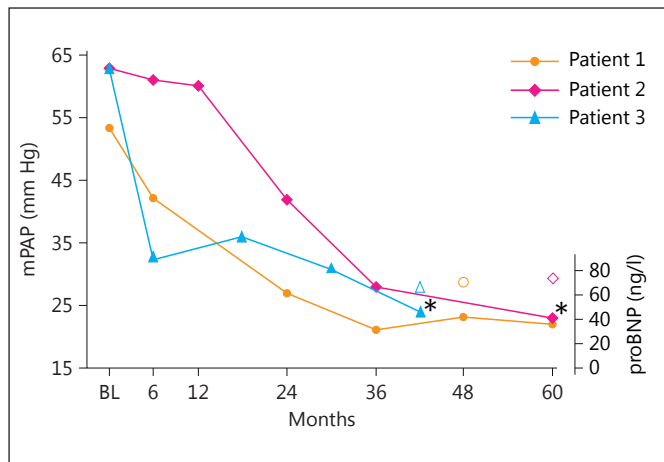
All 14 patients were followed up for 37 months (IQR 28–46; range 8–60). The 6MWD stabilized at a median of 455 m (IQR 412–550). Ten patients (71%; 95% CI 45–88) had a 6MWD >400 m at the last follow-up visit. The improvement in NYHA functional class remained signifi-

cant ( $p = 0.032$ ). Seven patients (50%; 95% CI 27–73) were still in functional class I–II at that time ( $p = 0.032$ ).

As shown in figure 2, health-related quality of life assessed by the CAMPOR questionnaire further improved to 9 points (IQR 7–27;  $p = 0.019$ ).

Taken as a whole, the mPAP remained 7 mm Hg lower compared to baseline, i.e. 46 mm Hg (IQR 31–58), but this did not reach statistical significance ( $p = 0.14$ ). How-





**Fig. 3.** Course of the mPAP in 3 patients. Except at baseline (BL) and month 6, the mPAP in patients 2 and 3 is based on echocardiographic assessments, calculated using the formula of Chemla et al. [16]. In both cases, the last echocardiograms were completely normal, with no measurable pressure gradient due to a lack of tricuspid insufficiency. For better visualization, a virtual value of 24 mm Hg was given at those time points (asterisks). On the right side, the corresponding proBNP levels at the last assessment are shown as open symbols.

ever, after a treatment period of 30, 32, and 44 months, respectively, in 3 cases the mPAP assessed invasively ( $n = 1$ ) or calculated from the echocardiographic pressure gradient ( $n = 2$ ) decreased by  $>30$  mm Hg to near-normal or normal levels (fig. 3), i.e. from 53 to 23 mm Hg, from 63 to 28 mm Hg, and from 63 to 31 mm Hg, respectively. The clinical course of the first patient has been described in detail elsewhere [13]. The latter 2 patients, in whom the mPAP was calculated from the systolic pressure gradient between the right ventricle and the right atrium, showed a completely normal echocardiography during follow-up without a measurable pressure gradient due the absence of tricuspid regurgitation. In addition, the levels of pro-brain natriuretic peptide (proBNP) were found to be normalized in all 3 patients. Though we had no invasive measurements in the latter 2 cases, these data taken as a whole may be indicative of ‘hemodynamic remission’ in 3 patients (20%; 95% CI 8–48).

In particular, there was a striking improvement in right ventricular function, which was assessed in 10 cases. The tricuspid annular plane systolic excursion and the fractional area change increased from 16 mm (IQR 14–18) to 21 mm (IQR 19–25;  $p = 0.01$ ) and from 20% (IQR 16–26) to 35% (IQR 29–42;  $p = 0.025$ ), respectively (fig. 4). Both of these 2 parameters normalized completely in 8 out of 10 patients (80%; 95% CI 50–94).

To compare the short-term hemodynamic effects with the long-term clinical parameters shown in table 3, we correlated them with the change in PVR within the first 6 months. However, except for a marginally modest Pearson’s  $r$  for the 6MWD ( $r = 0.54$ ) and the CAMPHOR ( $r = 0.50$ ), there was no relevant correlation whatsoever. Only 1 patient had a significant hemodynamic improvement, i.e. a decrease in mPAP of  $>10$  mm Hg to  $<40$  mm Hg. She belonged to the hemodynamic-remission group.

Three patients died after having been on targeted therapy for 50, 52, and 58 months, respectively, and on imatinib for 30, 46, and 47 months, respectively. The 2 patients who remained in NYHA functional class IV died after a rapid downhill course due to right heart failure. Interestingly, both patients showed all features known to be relatively specific for pulmonary veno-occlusive disease (i.e. a very low diffusion capacity, hypoxemia, and characteristic signs on chest computed tomography).

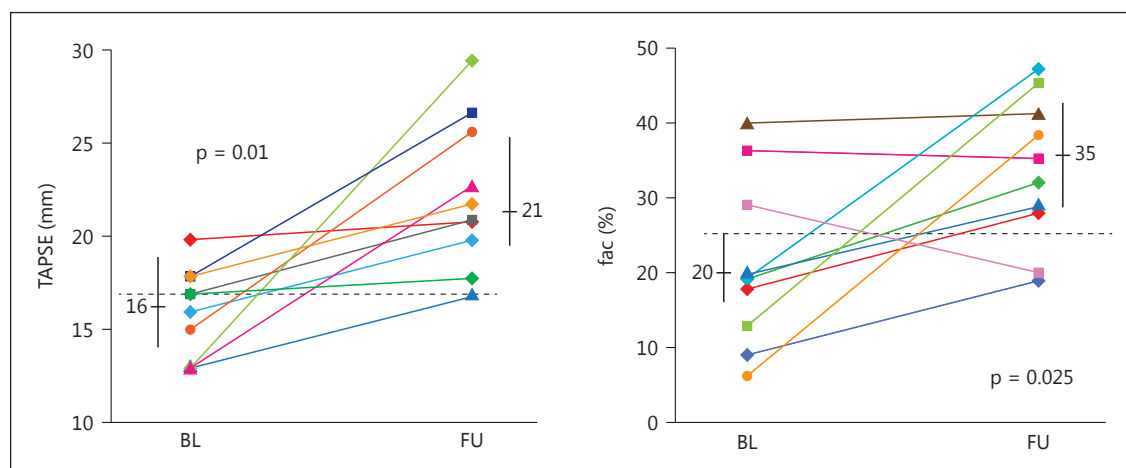
The third patient committed suicide because of a major depressive disorder. He was censored at that time. Hence, the overall 1- and 3-year survival was 100 and 90%, respectively.

#### Safety and Tolerability

Imatinib was generally well tolerated. The following complaints were noted: nausea ( $n = 4$ ), arthralgia ( $n = 4$ ), edema ( $n = 3$ ), abdominal pain ( $n = 2$ ), headache ( $n = 2$ ), and dizziness ( $n = 1$ ). One abnormality attributable to imatinib was a significant decrease in the total hemoglobin level from 13.7 g/dl (IQR 13.2–14.4) to 12.6 g/dl (IQR 12.4–13.6) after 6 months of therapy ( $p = 0.041$ ), with no change thereafter (12.6 g/dl; IQR 11.1–13.8). There was no evidence of cardiotoxicity. The pulmonary artery wedge pressure did not change during the first 6 months (table 2), and the left ventricular ejection fraction tended to increase from 63% (IQR 60–69) at the initiation of imatinib to 66% (IQR 63–68) at the last follow-up echocardiography ( $p = 0.066$ ; table 3).

Only after becoming aware of the association between imatinib and SDH based on the first presentation of the IMPRES data by Hoepfer et al. [17] in September 2011 was our attention drawn to 2 cases in our series who suffered from spontaneous SDH.

The first case occurred after 13 months of imatinib therapy in a 70-year-old female without a history of a preceding trauma. The duration of symptoms was 3 weeks. After surgical evacuation, the patient recovered without any neurological sequelae. Notably, the patient had suffered from an SDH on the contralateral side 3 years earlier when on oral anticoagulants only.



**Fig. 4.** Improvement in right ventricular function from baseline (BL) and the last follow-up visit (FU). Data are given as medians and IQR. The dotted lines indicate normal values. TAPSE = Tricuspid annular plane systolic excursion (in mm); fac = fractional area change (in %). Data were not available in 5 patients since their echocardiography was not performed at our institution.

**Table 3.** Efficacy parameters at baseline and at the last follow-up examination (n = 14)

|  | Baseline      | Last follow-up          | p     |
|--|---------------|-------------------------|-------|
| 6MWD, m  | 469 (413–514) | 455 (412–550)           | 0.820 |
| NYHA functional class (I/II/III/IV), n         | 1/12/1        | 1/6/5/2                 | 0.032 |
| CAMPOR score                                   | 29 (20–44)    | 9 (7–27)                | 0.019 |
| Mean pulmonary artery pressure, mm Hg          | 53 (42–63)    | 46 (31–58) <sup>a</sup> | 0.139 |
| Tricuspid annular plane systolic excursion, mm | 16 (14–18)    | 21 (19–25)              | 0.010 |
| Fractional area change, %                      | 20 (16–26)    | 35 (29–42)              | 0.025 |
| Left ventricular ejection fraction, %          | 63 (60–69)    | 66 (63–68)              | 0.066 |

Values are presented as medians (IQR) unless otherwise stated. <sup>a</sup> Calculated from echocardiography using the formula of Chemla et al. [16], except for 1 patient who underwent right heart catheterization.

The second patient was a 53-year-old female presenting with SDH after 2 months of imatinib therapy. Her symptoms started 5 days before the diagnosis when she had an INR of 5.4. In addition, at that time she was receiving continuous intravenous iloprost at a dose of 4.7 ng/min/kg. No surgical intervention was needed. In both patients, the oral anticoagulant was stopped but imatinib was continued.

Hence, the incidence of SDH in the current patient cohort was 2 per 37 patient-years (5%; 95% CI 2–18). After October 2011, we adjusted the INR to around 2.0, and thereafter no further SDH were observed. By the time of inclusion of our next 9 patients treated with imatinib, the

total safety follow-up time had accrued to 50 patient-years.

#### Patients' Decision Making

After becoming aware of the fact that imatinib by itself may contribute to the occurrence of SDH, we discussed this issue with our patients still on imatinib (n = 14) and oral anticoagulants (n = 12), as well as with the 9 subjects in the safety cohort.

As pointed out in Materials and Methods, the patients' decision making process was conducted by juxtaposing the maximum risk to be taken with the minimum potential benefit of continuing imatinib.

Regarding the maximum potential risk due to SDH, we confronted the patients with a worst-case scenario using the upper 95% CI. Hence, from our data mentioned above, which are comparable to those of the IMPRES cohort [22], the maximum annual risk of suffering from an SDH was estimated to be 18%. The maximum morbidity and mortality were calculated by multiplying this figure by the maximum inherent morbidity (8%) and mortality (3%) estimated from the literature data, as described in Materials and Methods. By rounding up the 95% CI of these 2 products, our scenario was an annual morbidity due to neurological sequelae of 2% and a mortality rate of 1%.

As outlined in Materials and Methods, for the NYHA functional class and the 6MWD we could tell our patients that they had at least a 25% chance of remaining in NYHA functional class I–II (the meaning of which they knew well from our standard questionnaire) and a 45% chance of retaining a 6MWD >400 m.

Confronted with this scenario in a narrative way, all patients were willing to take the worst potential risk-benefit ratio in favor of continuing the imatinib therapy. They all gave a second written informed consent including the issue of SDH. We counseled our patients to a target INR of around 2.0 and instructed them about the symptoms of SDH and the subsequent actions to be taken.

## Discussion

This is, to the best of our knowledge, the first report on a case series of long-term imatinib treatment in 15 patients suffering from far advanced PAH, with two thirds of the patients already on a triple targeted therapy including 6 cases on intravenous prostanoids. In line with the data from the phase II [23] and phase III [24] trials, there was a significant short-term improvement in functional class, health-related quality of life, and hemodynamics. The overall 1- and 3-year survival was 100 and 90%, respectively, which, in the context of the advanced stage of disease in our patients, is remarkable.

Over the long-term follow-up of a median of 37 months (range 8–60), possibly due to a ceiling effect, the 6MWD did not improve but remained at >400 m in 10 patients (71%). The NYHA functional class was still I–II in 7 patients (50%;  $p = 0.032$ ). Health-related quality of life, assessed by the CAMPHOR questionnaire, steadily improved from 29 points (baseline) to 20 points (after 6 months of imatinib therapy) and finally to 9 points (at the

end of follow-up) ( $p = 0.019$ ). It has to be mentioned that there were missing data for 5 patients due to linguistic reasons. This, however, should not have negatively influenced the results since 2 of these patients corresponded to the 3 cases attaining hemodynamic remission (see below).

Since we had data on the hemodynamic short-term response in 14 patients, we tried to correlate them by using the PVR as a fixed variable, with the parameters assessed in the long term. All correlations were trivial except that with the 6MWD ( $r = 0.54$ ) and the CAMPHOR ( $r = 0.50$ ). Hence, the short-term hemodynamic response could not predict the long-term outcome.

Three patients (20%; 95% CI 8–48) normalized their hemodynamic parameters assessed by invasive measurements ( $n = 1$ ) or echocardiography ( $n = 2$ ). The former patient could even be weaned from intravenous prostanoid therapy [13]. We recognize the important drawback insofar as that in the latter 2 cases we only had pressures derived from echocardiography. However, since both of them had a completely normal echocardiography with normal right ventricular function and no measurable pressure gradient on repeated occasions, as well as normalization of proBNP levels, these data indicate that both patients achieved hemodynamic remission.

Most notably, 8 out of 10 patients (80%; 95% CI 50–94) assessed by echocardiography showed complete normalization of right ventricular function. However, this has to be interpreted with caution since only 3 patients had normalized proBNP levels, and we had neither invasive hemodynamics nor assessments by MRI.

The drawbacks of the current study are obvious. Firstly, due to its open observational design, there was no control group for comparison with the imatinib-treated patients. Secondly, after the invasive assessment at 6 months of therapy, we had long-term right heart catheterization data for only 1 patient with hemodynamic remission. In another case, i.e. the sole patient who had no 6-month assessment, right-heart catheterization was repeated after 42 months on imatinib. By then her PVR had decreased from  $2,078 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$  at baseline to  $970 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ .

In comparison with the IMPRES trial [24], the current study has (aside from being noncontrolled) two differing aspects. Firstly, because of our relatively high treatment goals, the 6MWD in our patients was more than 100 m higher than in the IMPRES trial. Thus, in contrast to the latter, we could not show a significant improvement in the 6MWD, possibly due to a ceiling effect. Secondly, the PVR in the current cohort was almost  $600 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$  lower than in the IMPRES trial. Nine of our patients



would not have met the inclusion criterion for the IMPRES trial, i.e. a  $PVR > 800 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$ . Interestingly, even in this subgroup of patients there was a trend toward improvement in NYHA functional class ( $p = 0.14$ ) and quality of life ( $p = 0.07$ ). Although the number of cases was very small, this might indicate that imatinib potentially has a beneficial effect also in this less severely diseased patient group.

Imatinib was generally well tolerated even during long-term use. Besides a few transient complaints, there was a significant drop in hemoglobin values by 1 g/dl during the first 6 months, with no change thereafter. We could not detect any signs of cardiotoxicity. Only 1 patient definitely discontinued imatinib because of nonspecific complaints and the absence of a subjective benefit.

However, in September 2011 we became aware, from the first presentation of the IMPRES trial [17], that, as an unexpected and initially unrecognized complication of imatinib therapy, there is an increased risk of SDH in these patients. The authors of the study reported 2 cases of SDH while on imatinib during the randomized trial phase [24]. In addition, another 6 cases were observed in the extension study, summing up to an incidence of 4.2% per patient-year [22]. Hence, after receiving this information, we immediately took the following two measures.

Firstly, we confronted all of our current and the 9 subsequent patients treated with imatinib with a range of potential morbidity and mortality rates due to SDH and the potential, but actually unknown, benefits of imatinib. All patients were willing to take the worst risk-benefit scenario, and gave written informed consent to continue the imatinib therapy. They were explicitly informed about the first symptoms of SDH and the immediate measures to be taken, i.e. to go to the nearest hospital to perform a CT scan.

Secondly, we decided to retain oral antocoagulants in all our patients except in the 2 who had already experienced an SDH. However, we instructed them to keep their INR around 2.0. Thereafter, no additional case of SDH was observed over a period of 50 patient-years, including a safety cohort of an additional 9 patients.

The issue of oral anticoagulants in patients on imatinib is an important topic. A recent consensus paper of the working groups on pulmonary hypertension of the German-speaking countries [25] recommended avoiding oral anticoagulants in patients on imatinib. The decision to continue oral anticoagulants in the current cohort was based on our notion of aiming treatment at all 3 main pathogenic mechanisms leading to the progression of PAH, i.e. thrombosis, vasoconstriction, and proliferation.

Moreover, in light of the first report of Fuster et al. [26], which showed improved survival by more than 30% in patients on oral anticoagulants but without any targeted therapy, it is our belief that oral anticoagulants are crucial in these patients. This was recently corroborated by the data of the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPAREA), where a survival benefit of 10% could be demonstrated for IPAH patients on oral antocoagulants compared to those without [27].

Of course, we are fully aware that no firm conclusions can be drawn from the occurrence of 2 events out of a total of 15 patients, but these figures are in accordance with the IMPRES study and its open-label extension [22, 24]. In this cohort, an overall incidence of SDH of 5.7% (95% CI 3–10) was observed during a total of 160 patient-years. However, it has to be emphasized that, like in our 2 cases, a significant proportion of patients had additional risk factors for the development of SDH, like head trauma ( $n = 2$ ), concomitant intravenous prostaglandin therapy ( $n = 2$ ), a history of previous SDH ( $n = 1$ ), and acute myeloid leukemia with thrombocytopenia ( $n = 1$ ).

In the normal population, the incidence of SDH is between 0.0017 and 0.0034% per patient-year (weighted average 0.0025%) [28, 29]. It is mainly age dependent, with a 10-fold increase in patients aged  $> 65$  years (weighted average 0.026% per patient-year) [28–30]. Oral anticoagulants increase the risk by at least another 10-fold to 0.22–0.39% per patient-year, depending mainly on the level of the INR [31, 32]. In addition, Louis et al. [33] found an extraordinarily high incidence of 0.35% (95% CI 0.12–10) SDH cases in PAH patients on intravenous prostaglandin therapy and oral anticoagulants.

Hypothetically, the increased incidence of SDH during imatinib therapy might be explained by two facts. First, it is well known that tyrosine kinase inhibitors impair platelet aggregation in up to 85% of patients [34]. In addition, imatinib significantly decreases the stromal reaction and pericyte coverage of microvessels in colonic cancer [35]. This might result in an increase in vascular permeability and hence a propensity for bleedings during concomitant oral anticoagulants.

The morbidity and mortality of SDH is quite low and may be further reduced by the awareness of the patients and the knowledge of the actions to be taken in case of a sudden headache. From the upper 95% CI of the incidence of SDH during imatinib therapy (18%, see above) multiplied by the upper ranges of its morbidity (8%) and mortality (3%) as delineated in Materials and Methods, the maximum potential annual risk of SDH is 18%, lead-

ing to an annual serious morbidity of 1% and a mortality of 0.5%.

In conclusion, despite this being an uncontrolled trial, our data emphasize that treatment with imatinib might have important benefits and should be considered as an additional therapeutic option for patients with severe PAH.

## Conclusions

Though not powered for efficacy, the current study shows that long-term treatment of PAH with imatinib may not only stabilize the disease process but also lead to

a continued improvement in functional class, health-related quality of life, and normalization of right ventricular function. In a subset of patients, imatinib therapy might result in a hemodynamic remission. The occurrence of SDH in 5% of cases per patient-year is concerning. Nevertheless, the risk of significant morbidity and mortality from SDH is quite low, and keeping the INR around 2.0 might further minimize the risk of its occurrence.

## Financial Disclosure and Conflicts of Interest

The authors have no conflict of interests to disclose.

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